Functional Intestinal Disease

Introduction

This is a rapid-fire lesson that is functionally useful in clinical practice but tends to be on the lower-yield side of things for the licensing exams. Although it is far less focused on the cells and physiology, and more on the clinical application, it's still good to be exposed to this type of thinking at this early point in your training.

We first talk about a clinical approach to separating the types of diarrhea, then go into detail about each type. Diarrhea pharmacology is about helping patients with diarrhea to slow down the volume of their stool (except those with *C. diff*). We transition to megacolon as the segue into discussing constipation and ways to treat it. Then we close with the pharmacology of nausea.

Diarrhea

Diarrhea is defined as an increase in stool mass, frequency, or fluidity, typically greater than 200 g per day. In severe cases, stool volume can exceed 14 L per day and, without fluid resuscitation, result in death. Most cases of diarrhea are self-limiting and non-life-threatening. Diarrhea can be classified into three major categories:

TYPES OF DIARRHEA			
Factor	**Secretory**	**Invasive/Inflammatory**	**Osmotic/Malabsorption**
WBC/RBC	Negative	Positive	Negative
Changes with fasting	No change	No change	Stops with fasting
Osmolar gap	No osmolar gap	No osmolar gap	Huge osmolar gap
pH	Normal	Normal	Low
Pathogenesis	Isotonic secretion	Inflammatory cells in mucosa	Failure to absorb compound
Quality of diarrhea	High-volume diarrhea	Bloody diarrhea	Steatorrhea (fat) Or watery (anything else)

Table 13.1: Diarrhea Types
Separate the three types of diarrhea based on the osmolar gap, presence of inflammatory cells, and changes with fasting.

Secretory Diarrhea

The normal gut epithelium can secrete salt and water. The normal gut epithelium can absorb salt and water. The gut epithelium can only absorb or fail to absorb nutrients—there is no way for it to secrete proteins, fats, or carbohydrates into the gut lumen. This means that secretory diarrhea, caused by excess secretion from enterocytes, can be caused only by the secretion of electrolytes and water. This, in turn, means that there cannot be an osmotic gap—water would dilute the stool—nor should there be any excess cells—red blood cells or white blood cells. **Secretory diarrhea** is characterized by large-volume watery stool that does not change with fasting, has no cells, and no osmotic gap. It is caused by deranged **secretion of chloride** by crypt enterocytes that **exceeds the absorption of chloride** by the villi enterocytes.

There are endogenous compounds, called **secretagogues**, that stimulate secretion. These act through GPCRs. Some pancreatic neoplasms (VIPoma, serotonin-secreting carcinoid tumors) secrete excess secretagogues that cause secretory diarrhea, although they are very rare. However, we can use the familiar GPCRs and their second messengers (VIP with G_s, serotonin-secreting carcinoids with G_q) to set you up for success to understand how secretory diarrhea is caused by common infectious organisms. The leading causes of secretory diarrhea include infections with *E. coli* (the major cause of travelers' diarrhea), cholera (a cause of substantial morbidity and mortality in developing countries), and food poisoning in the United States due to *Staph. aureus* or *Bacillus cereus*—all produce enterotoxins (see Microbiology).

The enterocytes of the intestinal villi absorb. The cells of the intestinal crypts secrete. Normally, the rate of secretion by cells in the crypts is outpaced by the rate of absorption in the villi. But certain stimuli could result in an increased pace of secretion. There are multiple receptors and toxins, but only three common mechanisms. An enterocyte can be induced to secrete through an increase in cytoplasmic cAMP, cGMP, or calcium. **All three mechanisms end with the activation of a kinase.** Kinases add phosphates to things. When these kinases phosphorylate chloride channels, chloride passively moves down its concentration gradient and into the lumen. This electronegative charge is balanced by sodium, forming salt. Salt is osmotically active. Water is pulled from the interstitium to balance the osmotic load. "*Water follows salt.*" Even if there is no food entering the intestines, **isotonic fluid** is being secreted into the lumen faster than absorption can take it back in.

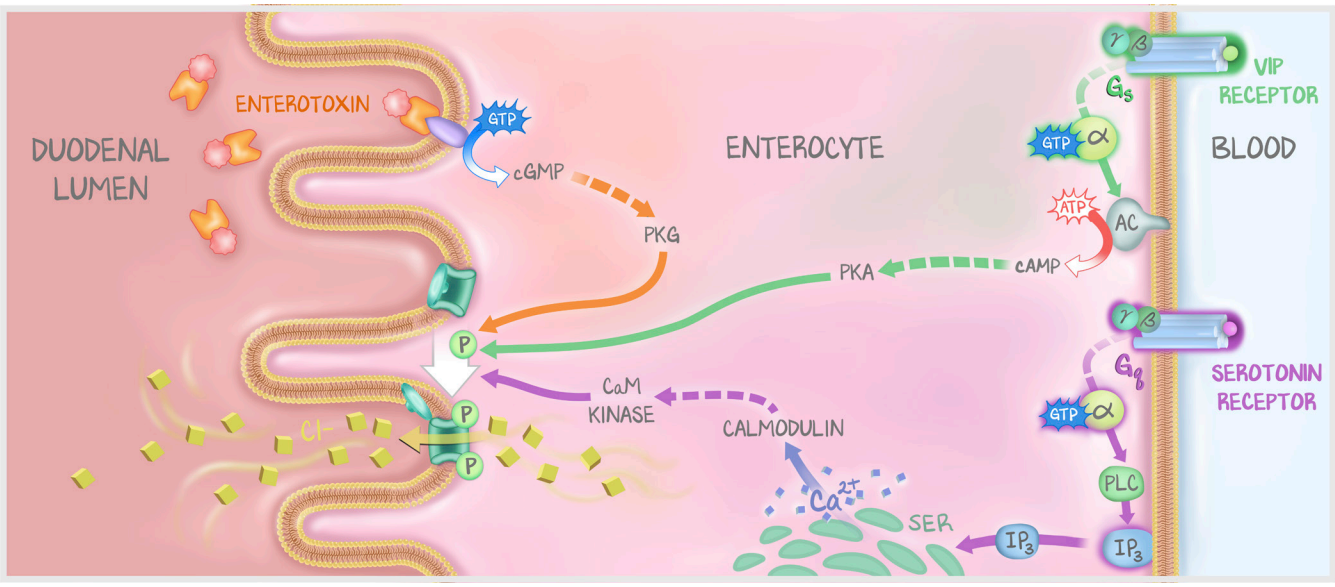

Figure 13.1: Mechanisms of Secretory Diarrhea
Secretagogues from the blood activate GPCRs. Serotonin activates a serotonin receptor and acts through G_q-IP3-Ca (with many steps removed for simplicity) to activate CaM kinase. Vasoactive intestinal peptide (VIP) activates VIP receptors, which act through G_s-AC-cAMP-PKA to activate protein kinase A (PKA). Luminal enterotoxins don't activate GPCRs, but act as guanylyl cyclase, making cGMP, which activates protein kinase G (PKG). Kinases add phosphates to things. Here, the phosphorylation (activation) of chloride channels is the initiating event, after which water follows. Excess activation of any of these mechanisms leads to secretory diarrhea.

Enterotoxins can act either as adenylate cyclase (increasing intracellular cAMP), as **cholera toxin** and ***E. coli* heat-labile toxin** do, or as guanylyl cyclase (increasing intracellular cGMP), as the ***E. coli* heat-stable enterotoxin** does. The rise in cGMP activates more PKG (a protein kinase activated by cGMP). The rise in cAMP activates more PKA (a protein kinase activated by cAMP). Both cause chloride channels to be phosphorylated, thereby opening those chloride channels, resulting in the release of chloride, sodium, and subsequently, water.

Although these mechanisms of increased secretion can lead to massively increased volume losses (cholera is fatal due to volume depletion if not treated), these mechanisms merely turn on more secretion. They do not turn off absorption. Sodium absorption is coupled to glucose absorption, both of which are osmotically active, and if either is absorbed, water will follow. Because the second messengers do not alter the function of glucose-coupled Na+ absorption, and because enterotoxin-mediated secretory diarrhea will self-resolve, administration of an **oral rehydration solution containing glucose and Na+** is effective in treating this form of diarrhea.

Osmotic Diarrhea

If a nutrient is not absorbed by the gut epithelium, that substance will exert an osmotic force on the gut lumen. It will pull water from the interstitium around the enterocytes into the gut lumen. It will also oppose the osmotic forces that accompany nutrient absorption. Water should follow salt. Water should follow glucose. Sodium is absorbed with glucose. The water should follow. Now, nothing special about salt or glucose makes water move with them; it's just that they are the predominant molecules in food that drive osmosis. Water follows the osmotic gradient. With salt absorbed but nutrients not, the water will stay in the gut lumen. Everything we ingest is osmotically active—proteins, carbohydrates, fats, and non-absorbable compounds. If our gut cannot digest the macronutrients into micronutrients and their constituent parts, our epithelium cannot absorb them. If there isn't an epithelium to absorb, absorption cannot happen at all. If we ingest something intentionally that our body cannot digest or absorb, it won't be absorbed. In every instance, **malabsorption** is the root of the problem. So . . . **malabsorption diarrhea** and **osmotic diarrhea** are the **same thing**.

This is an issue of nomenclature, not mechanism. When people say, "malabsorption diarrhea," they mean, "**fat** malabsorption." Fat malabsorption presents with **steatorrhea** and the subsequent impaired absorption of **fat-soluble vitamins (ADEK)**. Fat is an osmotic compound. Fat malabsorption results in osmotic diarrhea with steatorrhea and a loss of fat-soluble vitamins (ADEK). When people say, "osmotic diarrhea," they mean, "malabsorption of anything other than fats," so there is no steatorrhea and no absorption impairment of fat-soluble vitamins. This could be due to something as simple as lactase deficiency and dairy consumption (lactose intended on being digested and absorbed) or as severe as the ingestion of laxatives (never meant to be absorbed in the first place).

Regardless of whether it is fat or something else that isn't being absorbed, the key finding is a **high osmolar gap** and **cessation of diarrhea with fasting**. The calculated osmolar gap assesses what the stool osmoles should be if the osmolar load were just electrolytes. The calculation doesn't take into account any other substances. So if the measured osmoles are much higher than the calculated, something else is in the stool. That something else implies osmotic diarrhea. The presence of **high magnesium** suggests **laxative abuse**, whereas a **low pH** suggests **carbohydrate malabsorption**. The bacteria ferment the carbohydrates, lowering the lumen pH.

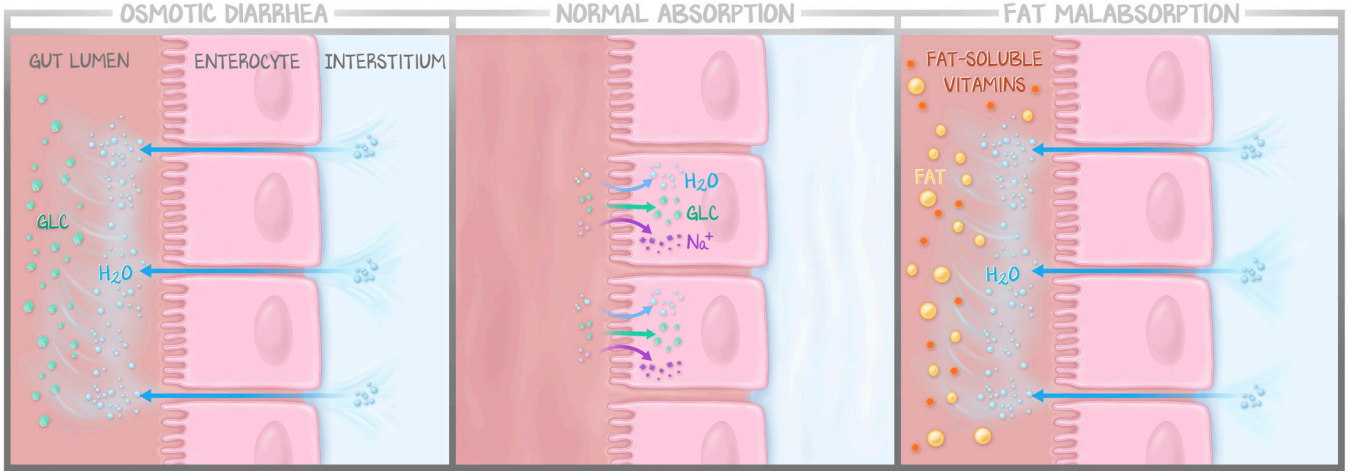

Figure 13.2: Osmotic Diarrhea
All osmotic diarrhea is some form of the inability to absorb a nutrient, resulting in osmotic load in the gut lumen. Malabsorption diarrhea refers specifically to fat malabsorption.

The causes of this type of diarrhea are vast. You should associate **lactose intolerance**, **celiac disease,** and **laxative abuse** with the causes of malabsorption that do not cause fat malabsorption. You should also associate **pancreatic insufficiency** and **Crohn's disease** with fat malabsorption specifically.

Inflammatory Diarrhea

Inflammatory diarrhea means one of two things: either **inflammatory bowel disease**, such as ulcerative colitis, or an infection with an **invasive organism**, such as *Shigella*. Inflammatory diarrhea is typically bloody diarrhea. Inflammatory bowel disease is often said to be a "diagnosis of exclusion." However, it is confirmed by biopsy, and therefore is not a diagnosis of exclusion. What people mean when they say "diagnosis of exclusion" is that the first time a patient presents with inflammatory diarrhea, rule out and treat the infection first, and only then after an infection has been ruled out, is it safe to pursue a diagnostic procedure.

The definition of inflammation is the presence of inflammatory cells in the mucosa. If a biopsy were done, you would see neutrophils, lymphocytes, or macrophages in the epithelium. Leukocytes will be present, whether it is inflammatory bowel disease or infection. But as we just said, you don't start with a biopsy. You start with stool studies. The hallmark of inflammatory diarrhea is **white blood cells** in the stool. Often, the inflammation provokes a friable mucosa, and so there are **red blood cells** in the stool as well. **Lactoferrin** is a superior test for red blood cells, and **calprotectin** is a better test for WBC. A **stool culture** with **ova and parasites** should be obtained. If positive for an infectious agent, that biopsy is not necessary. If negative for an infection, then the biopsy is obtained. Bloody diarrhea can occur without inflammation (ischemic colitis, for example). You should, however, learn that *inflammatory diarrhea is white blood cells and red blood cells in the stool.*

Bloody diarrhea can be remembered by "MESSY CACA."

	CAUSE	NOTES
M	Medical disease	Ulcerative colitis, ischemic colitis, radiation
E	Enterohemorrhagic *E. coli*	O157:H7, uncooked meat
S	*Salmonella*	Raw chicken/eggs
S	*Shigella*	Hemolytic uremic syndrome
Y	*Yersinia enterocolitica*	N/A
C	*C. diff*	Although *C. diff* toxin causes secretory diarrhea
A	*Amoeba histolytica*	HIV/AIDS
C	*Campylobacter*	Most common overall
A	*Aeromonas*	N/A

Table 13.2: MESSY CACA
The causes of bloody diarrhea and key associated notes.

Diarrhea Pharmacology

If there is a cause of the diarrhea—osmotic, invasive, medical disease—treat the cause. The vast majority of acute diarrhea in otherwise healthy patients is caused by viruses. It will run its course, and nothing need be done for the infection itself. Even when infected with an enterotoxin-producing bacteria, the disease is often self-limiting and non-life-threatening and needs only symptomatic relief. In these instances, there is **no physiological benefit to diarrhea**. It does not "flush the toxins out faster" or "remove the infection." Diarrhea of any kind only serves to dehydrate the patient. Therefore, any patient who has diarrhea should be given agents to slow intestinal motility to prevent dehydration and improve symptoms. **The only exception to this is *C. diff* colitis.** Even if *C. diff* colitis is NOT invasive, and is merely toxin-mediated, giving antidiarrheal agents to *C. diff* will result in megacolon. Treat the *C. diff* with antibiotics (oral vancomycin), and the diarrhea will slow. For everyone else, there are a few agents you can use to make the patient feel better and prevent dehydration.

The **antimotility** agents are modifications of meperidine and are μ **(mu)-opioid stimulators**. These bind to presynaptic μ receptors, which inhibit the release of acetylcholine from the enteric nervous system, thereby reducing peristalsis, thereby reducing motility. The two examples of this are **diphenoxylate** and **loperamide**—they **slow gut motility**. If too much is taken, opiate-induced constipation may occur. Because these drugs are available over the counter, some patients experiencing opiate withdrawal may attempt loperamide ingestion to alleviate the withdrawal effects and end up with megacolon instead.

Bismuth, the thing we use to coat the ulcer base in peptic ulcer disease, also has some effect on diarrhea. The mechanism is unclear. Just remember, "Bismuth, PUD, turns stool black," and, "somehow also helps diarrhea."

Octreotide in depot form can be used to treat secretagogue-based chronic diarrhea.

Adsorbents—methylcellulose and aluminum hydroxide—should be avoided. They presumably bind up some toxins but are far less effective than antimotility agents. Adsorbents also indiscriminately adsorb and can affect the absorption of other medications.

That means for symptomatic relief of acute diarrhea, there are μ-opiate receptors and bismuth. That's it.

Megacolon

Megacolon is defined as a segmental or total dilation of the colon. **Toxic megacolon** is a complication of inflammatory bowel disease colitis or *C. diff* colitis that presents with megacolon (nonobstructive dilation of the colon) with systemic toxicity (fever, leukocytosis, sepsis, hypotension). Megacolon is a word that gets thrown around because it means, "this is bad" and "the risk for perforation is high." It isn't a pathophysiological process, but rather a radiographic finding with prognostic implications.

There are two similar forms of megacolon (not toxic)—Hirschsprung's disease and Chagas disease.

Hirschsprung's disease is also called **congenital megacolon**. The colon will appear dilated (megacolon) if a barium enema is performed. But the main presentation will be a **failure to pass meconium**. This is a congenital disease whereby the distal colon **lacks the autonomic ganglia** of the **myenteric plexus.** Their absence is a result of the **failure of neural crest cell migration**. This is a distance thing—everything from the most proximal affected segment of the colon distally to the anal canal will be affected. Visualize the gut tube, mouth on top, anus on the bottom. Neural crest cells have to migrate from the mouth end of the gut tube down to the anus end of the gut tube. However far they make it is how far they make it, and there won't be any neural crest cells past the farthest-migrated cell.

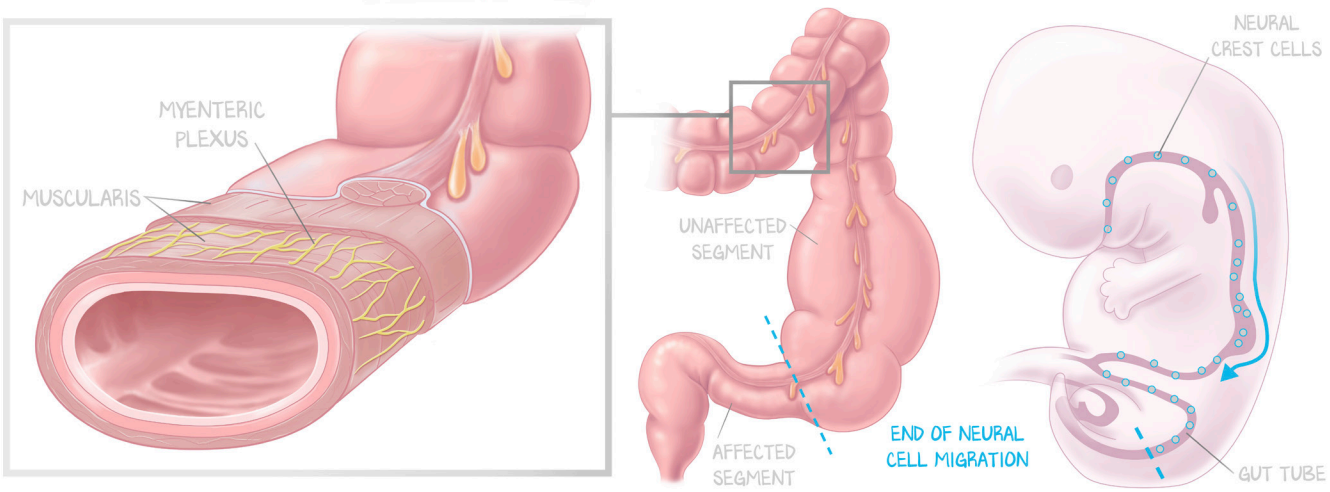

Figure 13.3: Hirschprung's Disease Illustrated
Neural crest cell migration creates the peripheral nervous system and becomes the ganglia and post-ganglion neurons. The myenteric plexus represents the location of the parasympathetic ganglia. We'll cover this in more detail in Neuroscience, but essentially, neural crest cell migration occurs sequentially. Because the distal large intestine (technically the anal canal, but we're depicting the colon for ease of illustration) is the farthest away from the cells' origin, neural crest cell migration to these tissues happens last. And if the neural crest cells fail to migrate to one segment, they don't have the chance to migrate to the remaining (more distal) segments. So wherever the migration fails represents where the myenteric plexus ends. Thus, congenital megacolon is always caused by a defect at the distal end, from the site of the failure to the anus. Without a myenteric plexus, there can be no movement. Without movement, stool accumulates in the unaffected proximal colon, which distends.

The myenteric plexus is what makes the muscles of their segment contract. Without a myenteric plexus, there will be no mass movements or haustrations. No movement through the affected segment. The tube itself is intact, but the ability to move stool along the tract is absent. The unaffected segment contracts, the stool doesn't move, and so the affected colon undergoes receptive relaxation. That means the **unaffected segment is dilated**, whereas the **affected segment appears normal**. Neurons will never migrate, so the affected segment must be **resected**. This form of megacolon is associated with mutations of the *RET* gene and Down syndrome.

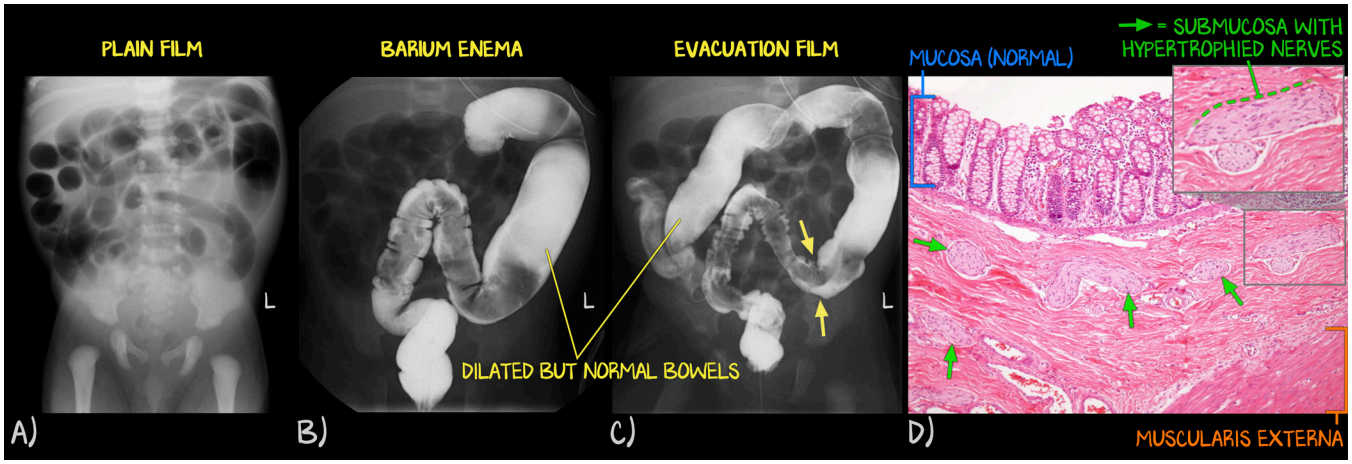

Figure 13.4: Hirschprung's Disease
(a) Plain film of a neonate with failure to pass meconium showing numerous air-fluid levels, indicative of obstruction. (b) Barium enema revealing a distal, normal-appearing rectum and sigmoid colon and a dilated unaffected bowel that appears to be without haustrations, resulting from distention. (c) Evacuation film showing that the entire proximal colon is affected and demonstrating the transition point more clearly (white arrows). (d) Suction biopsy revealing a normal mucosa, normal muscularis externa (not seen), and a submucosa with hypertrophied nerves (usually not visible).

Chagas disease is caused by chronic infection with the parasite *Trypanosoma cruzi* (the same infection that takes the myenteric plexus of the esophagus and causes achalasia) and takes the myenteric plexus of the colon. And as we said in the achalasia lesson, any myenteric plexus may be affected—esophageal, colonic, intestinal, uterine. A biopsy will show *T. cruzi* in the muscularis externa and a deficient myenteric plexus. Chagas disease is classically a disease of South America. Those who have it in the United States likely spent several decades in South America, acquired the infection, then spent several decades in the United States.

***C. diff* colitis** can present with **toxic megacolon**. This is discussed in the Microbiology module. In short, this is the worst form of *C. diff* colitis. Treatment with oral vancomycin and intravenous metronidazole is indicated. If paralytic, surgical resection may be required. **Ulcerative colitis** can present with **toxic megacolon**. This is discussed in the lesson on intestinal inflammation.

Constipation Phys and Pharm

Constipation can be caused by one of two things, though they are usually synergistic: too little water and too little movement.

Too little water. The colon absorbs water. The longer the stool sits in the colon, the more water is absorbed. Unlike the bladder, you can voluntarily control the colon and hold in stool—until you get a fecal impaction and need surgery to relieve it or your colon perforates. If the stool becomes too depleted of water, it becomes hard and solid. Passing a football through your anus does not sound fun, does it? Especially when that football is made of concrete. Receptive relaxation allows more stool to fit in the rectum, so the stool is large in volume (football). The colon absorbs the water, so the stool is really hard (concrete).

Too little movement. Haustral contractions are the segmental distention and contraction of the colon. They serve a similar purpose to the churning and segmentation of the small intestine. They make sure the stool's nutrients are absorbed by increasing the surface area exposed to the epithelium. The propulsive movement is generated by a **mass movement**, the colon's version of peristalsis. This engages the longitudinal muscles. Like everywhere in the GI tract, this is mediated by the enteric nervous system

and the release of ACh onto M_3 receptors. This stimulates the colon to contract. The motility is weak in the colon in the first place, so even small degrees of spasm or motility inhibition have a big impact. Infants are incontinent of stool. They learn to control it in potty training. You CAN hold in your stool. You shouldn't.

Preventing defecation when the defecation reflexes are excited, or if one overuses laxatives to take the place of natural bowel function, will cause those natural reflexes to progressively weaken. It takes months to years, but a colon can become *atonic*. Maintaining regular bowel habits prevents constipation later in life.

The reason for this longwinded discussion of constipation is so that you remember to a) **prophylax against constipation** and b) treat with a **combination** of **motility** agents and **bulking/laxative** agents. Stimulating the colon to contract against a concrete football only causes pain. Softening the stool but having no motility just lets a puddle sit there waiting to shoot out all over the place. The goal should be to soften the stool and give the colon's motility a little push.

Prophylaxis is with good bowel habits and a high-fiber diet. Dependence develops if laxatives are used too long. Get people eating, moving, and pooping. When that fails, the table below shows what does what. You will develop practice patterns—drug choices—based on where you train. No one choice is better than another.

Opiate-induced constipation is a specific type of constipation that is caused by the stimulation of μ receptors in the peripheral enteric nervous system. μ Receptors prevent the release of acetylcholine. If the patient is going on opiates, initiate treatment before they get opiate-induced constipation. You should use a combination of **stool softeners** (docusate) and **motility agents** (senna) for opiate-induced constipation prophylaxis. If the patient is already on opiates and has opiate-induced constipation, you can undo the damage with peripheral μ antagonists, such as methylnaltrexone. There isn't one preferred method, and each practice location will have its own practice patterns.

Ogilvie's syndrome is a type of large-bowel obstruction that occurs in old people. It is temporary, and stimulating the bowel with an acetylcholinesterase inhibitor (neostigmine, see General Pharmacology #9: *Cholinergics (PNS)*) can overcome it.

ROUTINE USE			
TYPE	**MECHANISM**	**EXAMPLES**	**NOTES**
Osmotic laxatives	Causes osmotic diarrhea	Magnesium hydroxide Magnesium citrate Lactulose	Abused by patients with bulimia, if diarrhea and magnesium in stool, consider these
Bulk-forming laxative	Soluble fiber draws water into the gut lumen, promotes peristalsis	Psyllium Methylcellulose	Causes bloating
Lubricant laxatives	Lubricates hard stool to make passage less painful; does nothing for motility or water	Mineral oil (oral) Glycerin (suppositories)	Really bad for lungs if aspirated
Motility laxatives	Both are irritants; bisacodyl also activates enteric nerves	Senna Bisacodyl	Melanosis coli (pigmentation of the colon)
Stool softeners	Emulsifies with the stool to make it softer	Docusate	Prophylaxis rather than treatment, takes days
SPECIFIC USE			
TYPE	**MECHANISM**	**EXAMPLES**	**NOTES**
Muscarinic agonists	Acetylcholinesterase inhibitor, leads to M_3 activation	Neostigmine	Used for Ogilvie's syndrome
Opiate receptor blocker	Pure opiate antagonist, only of peripheral opiate receptors	Methylnaltrexone Naloxegol	Does not block the effect of pain relief
Chloride channel stimulator	Causes cholera diarrhea	Lubiprostone	Only for refractory chronic constipation

Table 13.3: Constipation Medications
Some medications are routinely used, and some carry specific uses for specific diagnoses.

Antiemetics

Vomiting, a frequent sign and symptom in clinical medicine, indicates the need to induce emesis and then coordinate the action of emesis. **Nausea** is the sensation that vomiting may occur. The act of **emesis** involves several preprogrammed coordinated muscle responses (kept vague; don't learn them).

Signals from four general centers throughout the body carry inputs to the **vomiting center** in the **medulla**. This center coordinates the initial motor mechanisms of emesis. Inputs from the **gastrointestinal tract** caused by irritants and distention (presumably to expel the irritants) are sent by the **vestibular system**, and inputs from the **chemoreceptor trigger zone (CTZ)** have well-established links. The fourth is from the **cortex**, which can provoke vomiting with increased intracranial pressure, anxiety, or pain. This pathway is less well understood.

In general, we don't want to stop emesis caused by an irritant or distention in the GI tract, but we do want to limit motion sickness (vestibular system) and side effects of medications, such as chemotherapy (CTZ). So, many of our therapies focus on the CTZ and vestibular system.

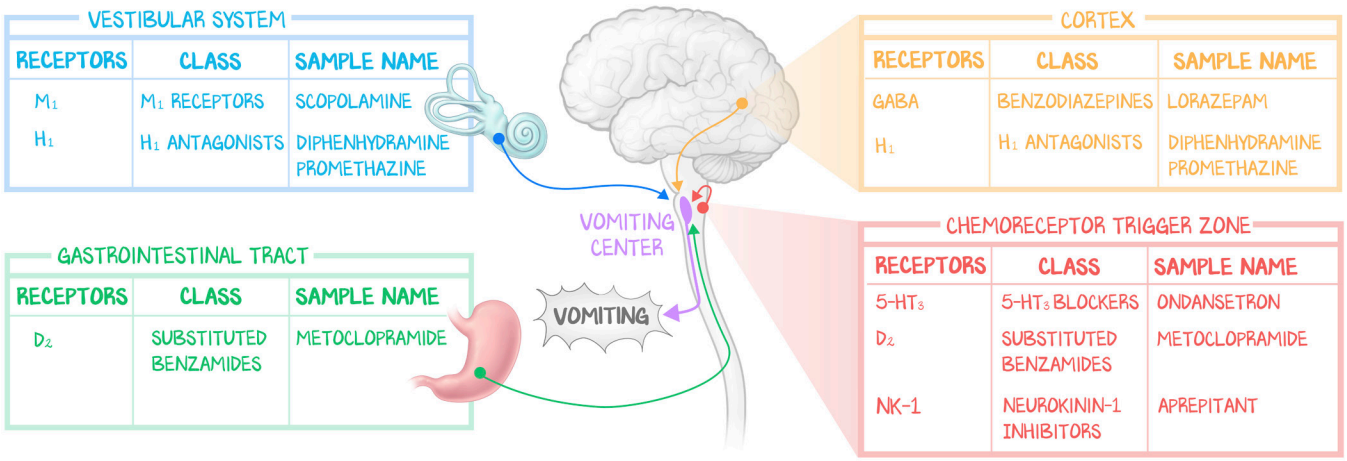

Figure 13.5: Emesis
The vomiting center coordinates nausea and vomiting. It has four inputs. The first input is from the vestibular system. Vestibular causes of nausea are vertigo and motion sickness. Blocking M1 receptors (scopolamine) and H1 receptors (promethazine) in the vestibular apparatus reduces vertigo and nausea from motion. The gastrointestinal tract, which responds to irritants and toxins in the gut, is the second input. Prokinetic drugs, such as metoclopramide, can be used to quell nausea and get the gut moving. The third is the chemoreceptor trigger zone. Drugs and chemotherapy affect the CTZ and are the main targets of antiemetic manufacturing. 5-HT3 blockers (ondansetron) and NK-1 antagonists (aprepitant) are key players here, whereas metoclopramide also has some effect. The fourth input is the cortex, which contributes in a less well-understood way, but benzos make for exceptional adjuncts (used off-label). Not on this illustration are systemic corticosteroids.

The **chemoreceptor trigger zone** is also known as the *area postrema* and exists at the caudal end of the fourth ventricle. There, dopamine (**D_2**), serotonin (**5-HT_3**), and neurokinin (**NK-1**) receptors stimulate this area. This area is responsible for nausea and vomiting caused by medications, such as chemotherapy, and coordinating the vestibular input of motion sickness. Electrically stimulating this region induces vomiting. Blocking receptors here does prevent the medication-induced emesis, but does not change the response due to noxious stimuli in the gut.

Antiemetics target receptors. Most of the medications we have made are for chemo-induced emesis, and so target the CTZ rather than the vomiting center. Other medications target the vestibular system directly.

CLASS	SAMPLE NAMES	RECEPTORS	ZONE	NOTES
5-HT_3 blockers	Ondansetron	5-HT_3 blocker	CTZ	Chemo- and GI-induced issues Does nothing for vestibular causes
Substituted benzamides	Metoclopramide	D_2 blocker	CTZ Gut	Chemo- and GI-induced Prokinetic agent in the gut Causes extrapyramidal symptoms tardive dyskinesia, as well as tolerance
NK-1 inhibitors	Aprepitant	NK-1 blocker	CTZ	Chemo-induced
Corticosteroids	Dexamethasone Methylprednisolone	Unknown	All	Maximum therapy usually used in conjunction with something else
Benzodiazepines	Alprazolam Lorazepam	GABA stimulation	Cortex	For this stage of training, they "don't work" for nausea.
M_1 Receptors	Scopolamine	M_1 agonists	Vestibular Apparatus	Motion sickness, memory loss
H_1 antagonists	Diphenhydramine Promethazine	H_1	Vestibular Apparatus Cortex	Motion sickness, causes sedation

Table 13.4: Antiemetics
Organized by class, receptor, and the zone they affect.

Citations

Figures 13.4a, 13.4b, 13.4c: Courtesy of Radiopaedia.com.

Figure 13.4d: Courtesy of WebPathology.com.